The Synthesis and Chemiluminescence of an Amino Derivative and a Sulfur Analog of Luminol

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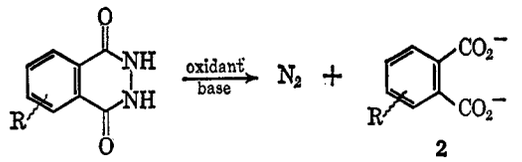
A diaminophthalic hydrazide (**8**) has been synthesized in seven steps from chloronitrophthalimide. The compound proved to be only about one-third as efficient in light production as luminol (**3**). A sulfur analog of luminol, 4-dodecanethiophthalic hydrazide (**38**), was also prepared and tested. Contrary to a report in the literature, the oxidation of 5,6-dimethylbenzimidazole yields principally 5-methylbenzimidazole-6-carboxylic acid and not benzimidazole-5,6-dicarboxylic acid (a potential precursor in the synthesis of compound **8**).

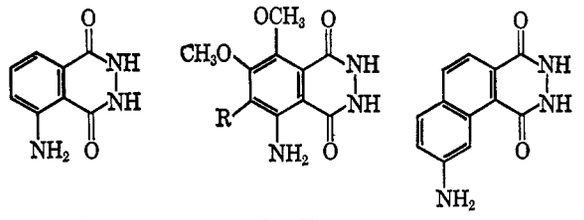
Chemiluminescence of the cyclic hydrazides (**1**) involves an oxidation to the corresponding phthalate ion (**2**), which is the light-emitting species in the reaction.[1]



1 **2**

The efficiency of light emission is increased by electron-releasing substituents,[2] an effect also noted in the chemiluminescence of the imidazoles[3] and the indoles.[4] This effect results largely from the ability of electron-releasing substituents to increase the fluorescence quantum yields of the light emitters, *e.g.*, **2** in the hydrazide chemiluminescence. The over-all effect had been noted earlier,[5] but at that time it was thought that the hydrazides (**1**) were the light emitters.

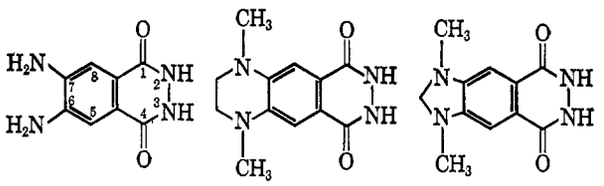
Of the substituents that have been employed, the amino function leads to the most efficient chemiluminescent hydrazides and in fact until very recently luminol (**3**), the very compound with which Lommel[6] discovered the chemiluminescence of the hydrazides, was the most efficient of the many analogs that had been tested. Recently, however, the methoxy derivatives (**4** and **5**)[7] and the naphthalic analog of luminol (**6**)[8] have been found to have higher quantum yields in chemiluminescence than luminol.



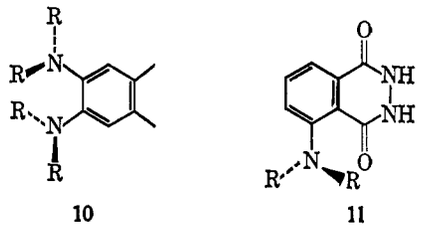
3 **4**, R=H; **5**, R=CH_3O **6**

The rationale behind the present work was that two amino functions on a single ring might lead to hydrazides still more efficient than luminol. Actually, three of the possible diaminophthalic hydrazides (**7** and the 5,7 and 5,8 isomers)[5,9] had already been synthesized and tested. However, in common with the phenylenediamines, these compounds are degraded by the oxidizing agents used in the chemiluminescence, and black condensation products are formed which mask the true light-emitting ability of the hydrazides; in fact, compound **7** and the other isomers were far less efficient in light production than luminol itself.

Because of this overoxidation, we decided to use fully substituted amino groups. This decision led to ring derivatives **8** and **9**, since molecular models show that dialkylamino groups in an *ortho* relationship to one another and to the carbonyl group have serious nonbonded interactions that lead to a twisting of the dialkylamino groups out of the molecular plane (**10** and **11**). This noncoplanarity would be expected to decrease the delocalization of the electrons of the amino group over the aromatic ring, and to decrease the effectiveness of the groups in chemiluminescence; in fact, dimethylluminol (**11**, R = CH_3) has a chemiluminescence efficiency approximately that of phthalic hydrazide (**1**, R = H).[10]



7 **8** **9**



10 **11**

The successful synthesis of **8** is given in Scheme I. All the reactions went smoothly, although low yields were obtained in the second step of the sequence.

Compound **19**, the nonmethylated analog of **8**, was also prepared since imide **17** was available.

A different, earlier approach to **8** failed because of our inability to mononitrate N-methyl-4-aminophthal-

(1) E. H. White, O. Zafiriou, H. M. Kagi, and J. H. M. Hill, *J. Am. Chem. Soc.*, **86**, 940 (1964); E. H. White and M. M. Bursey, *ibid.*, **86**, 941 (1964). K. D. Gundermann [*Angew. Chem. Intern. Ed. Engl.*, **4**, 566 (1965)] has given other examples confirming that the acid anions are the light emitters.

(2) A. Spruit-Van Der Burg, *Rec. Trav. Chim.*, **69**, 1536 (1950).

(3) G. E. Philbrook and M. A. Waxwell, *Tetrahedron Letters*, 1111 (1964); E. H. White and M. J. C. Harding, *Photochem. Photobiol.*, **4**, 1129 (1965); *J. Am. Chem. Soc.*, **86**, 5686 (1964).

(4) F. McCapra, D. G. Richardson, and Y. C. Chang, *Photochem. Photobiol.*, **4**, 1111 (1965).

(5) H. D. K. Drew and F. H. Pearman, *J. Chem. Soc.*, 586 (1937).

(6) As reported by H. O. Albrecht, *Z. Physik. Chem.*, **136**, 321 (1928).

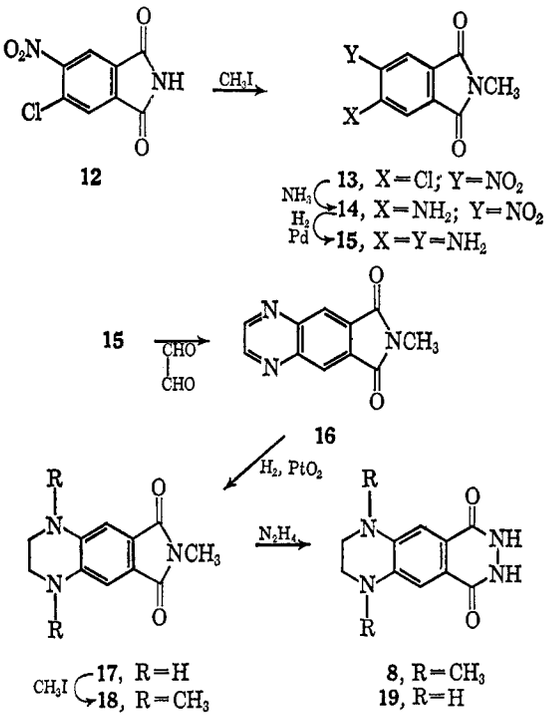
(7) E. H. White and M. M. Bursey, *J. Org. Chem.*, **31**, 1912 (1966).

(8) K. D. Gundermann, W. Horstmann, and G. Bergmann, *Ann.*, **684**, 127 (1965).

(9) R. Wegler, *J. Prakt. Chem.*, **148**, 135 (1937).

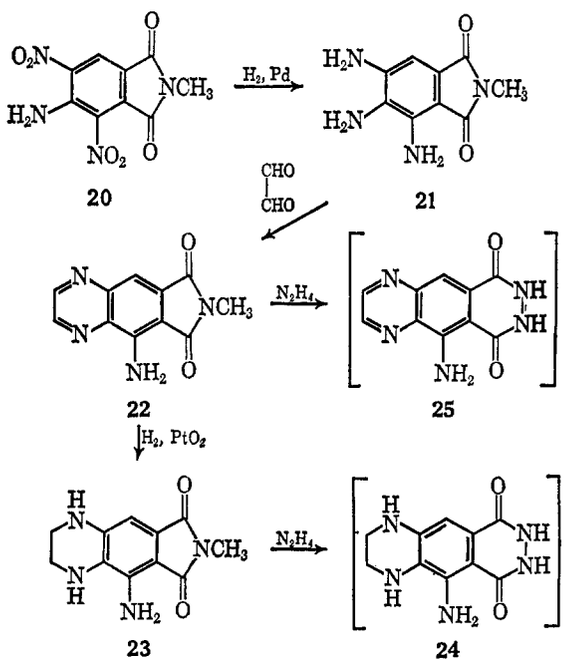
(10) K. D. Gundermann and M. Drawert, *Chem. Ber.*, **95**, 2018 (1962); this effect was also found independently by J. H. M. Hill in our laboratory.

SCHEME I



imide to give **14**;[11] dinitration occurred instead to give **20**. In view of later experience in the nitration of 2-aminobiphenyl, it is possible that the use of stoichiometric amounts of nitric acid might have led to mononitration. In any case, **20** was treated as shown in Scheme II in attempts to prepare analogs of **8**; the two hydrazides (**24** and **25**) could not be obtained analytically pure, however. Compound **22** is believed to have the structure shown rather than that derived from the condensation of glyoxal with the 3- and 4-

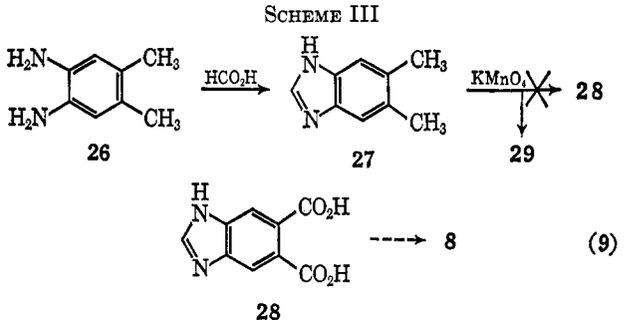
SCHEME II



amino groups of imide **21**, since it displayed bands in the infrared at 1750 and 1700 cm^{-1}. The analog, 3-aminophthalimide, had bands at 1750 and 1720 cm^{-1}. On the other hand, 4-aminophthalimide absorbed at 1770 and 1720 cm^{-1} and compound **16** at 1770 and 1725 cm^{-1}. The shift in carbonyl frequency by the amino groups in the 3 position is probably a result of hydrogen bonding.

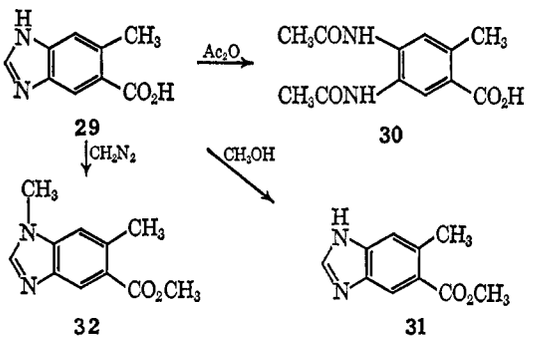
In a third approach to the fully alkylated hydrazides, we attempted the synthesis of **8** by the sequence shown in Scheme III. Benzimidazole-5,6-dicarboxylic acid

SCHEME III



(**28**) had been reported by Morgan[12a] from the oxidation of 5,6-dimethylbenzimidazole (**27**). We repeated the oxidation and obtained a product with an infrared spectrum essentially identical with that of a sample kindly supplied by Professor Morgan;[12a] the elemental analyses, furthermore, were close to the calculated values for the monohydrate of the desired compound. However, the nmr spectrum of the oxidation product clearly showed the presence of a methyl group. Subsequent analyses were variable and fractional crystallization led to samples with slightly different infrared spectra. Although the substance gave a negative Beilstein test, an elemental analysis showed the presence of chlorine (an artifact of the method of isolation–acidification of a basic solution of the acid with hydrochloric acid). The presence of submolar amounts of chlorine accounted for the previous difficulties with the elementary analyses. Recrystallization of the material from hydrochloric acid then yielded the analytically pure monohydrochloride of 5-methylbenzimidazole-6-carboxylic acid (**29**). Because of these difficulties, the further oxidation of **29** was not thoroughly investigated. Derivatives **30–32** were prepared in early efforts to determine the constitution of compound **29** (see Scheme IV).

SCHEME IV



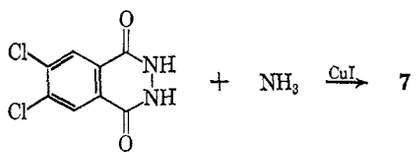
(11) We used, among others, the conditions under which 3-amino-N-methylphthalimide was successfully nitrated to yield 3-amino-6-nitro-N-methylphthalimide (M. M. Rauhut, *et al.*, Technical Report No. 1, Chemiluminescent Materials, American Cyanamid Company, Stamford, Conn., 1963.

(12) (a) K. J. Morgan, *J. Chem. Soc.*, 2343 (1961). (b) A successful oxidation of 2,3-dihydroxy-6,7-dimethylquinoxaline to the dicarboxylic acid has been reported recently [Y. W. Chang, French Patent 1,386,355 (Jan 22, 1965); *Chem. Abst.*, **62**, 14702 (1965)].

The oxidation of 6,7-dimethylquinoxaline (**33**) was also attempted in still another approach to **8**, but the reaction led to the monocarboxylic acid (**34**) and several unidentified compounds.[12b]

33 **34**

In a fifth approach to **8**, we followed the directions of Drew and Pearman[5] for the synthesis of 4,5-diaminophthalic hydrazide (**7**), with the view in mind of converting it to **8**. In our experiments, four compounds were formed, and, since not even the analogous reaction of 4-chlorophthalic hydrazide proved straightforward, this approach was abandoned. It should be pointed out that although a satisfactory analysis had been reported[5] for compound **7**, it is not clear whether the product was a pure compound or a mixture of isomers.

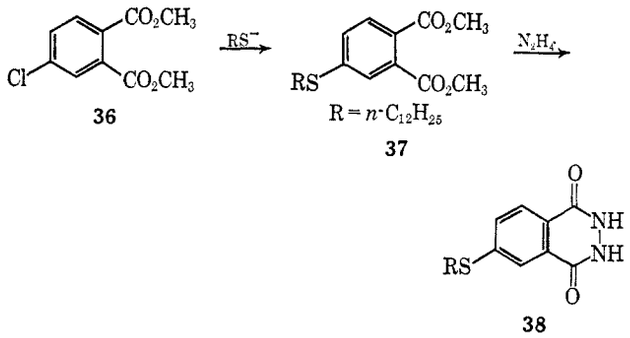


35

Chemiluminescence Results.—Two different solvent systems have been used to date in studies of the chemiluminescence of the hydrazides.[13] Aprotic solvents (of which dimethyl sulfoxide appears to be the best) plus the reagents oxygen and a base lead to the highest quantum yields for methoxy derivatives of luminol.[7] Luminol itself, on the other hand, gives the same amount of light in DMSO as in the protic solvent water,[14] where hydrogen peroxide, base, and hemin are required for chemiluminescence. The reasons for these variations are not known at the present time; it appears, however, that only compounds with ionizable amino and hydroxy groups are efficient in the DMSO system. In any case, **8** gives very little light in DMSO, and in water it yields only about one-third as much light as luminol. As expected, **19**, **24**, and **25** gave colored products and very little light in both protic and aprotic systems. It appears, therefore, that highly efficient derivatives are not to be found in the phthalic hydrazide series, and that larger ring systems will be needed (*e.g.*, as in compound **6**).

6-Dodecanethio-2,3-dihydrophthalazine-1,4-dione (38).—Since amino and alkoxy substituents increase the chemiluminescence ability of phthalic hydrazide, it was of interest to determine the effect of sulfur-containing substituents. A thioether derivative of phthalic hydrazide was synthesized as shown in Scheme V. The compound proved to be far less efficient in light production than either the corresponding 4-amino analog or 3-hydroxyphthalic hydrazide, the most closely related oxygen analog known (both the dimethyl sulfoxide and water–hemin systems were used).[13]

SCHEME V



36 **37** **38**

Experimental Section

Starting Materials.—Sodium phthalate was chlorinated by the method of Ayling[15] and the product was esterified with methanol (sulfuric acid catalyst) by refluxing the mixture for 1 day. Fractionation of the methyl esters yielded dimethyl 4-chlorophthalate (**36**) (30–40% yields; nmr, ABX pattern (3 H) centered at τ 2.25 and a singlet (6 H) at 6.04) and dimethyl 4,5-dichlorophthalate (1–2% yields; nmr, singlet (2 H) at τ 2.12 and singlet (6 H) at 6.08). Treatment of the esters with hydrazine yielded the mono- and dichlorophthalic hydrazides as described by Drew.[5] Reaction of the monochlorohydrazide with ammonium hydroxide in the presence of cuprous iodide at 180° for 16 hr yielded a mixture of two compounds (R_f 0.35 and 0.43) as shown by paper chromatography with an alcohol–ammonia–water mixture (8:1:1). The R_f 0.43 compound was shown to be 4-aminophthalic hydrazide; the other compound was not starting material (R_f 0.60), dichlorophthalic hydrazide (R_f 0.69), or luminol (**3**, R_f 0.48). The reaction of the dichlorophthalic hydrazide (**35**) with ammonia under the conditions reported by Drew[5] yielded a small amount of a mixture of four compounds, as shown by paper chromatography.

4-Chloro-5-nitrophthalimide (12).—The saponification of dimethyl 4-chlorophthalate yielded 4-chlorophthalic acid, mp 150–151° (lit.[15] 150–150.5°), which was converted,[16] *via* the ammonium salt, into the imide, mp 201–205° (lit.[17] 210–211°). Nitration then led to 95% yields of 4-chloro-5-nitrophthalimide, mp 201–202° (lit.[18] 198–200°).

4-Chloro-5-nitro-N-methylphthalimide (13).—To a solution of 4-chloro-5-nitrophthalimide (9.8 g, 43 mmoles) in 100 ml of acetone was added 10 ml of methyl iodide and 10 g of potassium carbonate, and the mixture was refluxed for 1.5 hr. The reaction mixture was filtered while hot and the orange filtrate was condensed to one-fourth volume, then kept at 5° for 10 hr to give 5.1 g of colorless needles. The mother liquor was condensed to give an additional 3.1 g of product. Both crops were combined and recrystallized from methanol to give 7.9 g (33 mmoles, 77%) of colorless needles, mp 168–170°. Three recrystallizations from methanol gave a sample that had mp 171–172°; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 210 mμ (log ϵ 3.88) and 296 (4.01); nmr singlets at τ 1.79, 1.98, and 6.76 (in weight ratio 1:1:3).

Anal. Calcd for $C_9H_5ClN_2O_4$: C, 44.92; H, 2.19; N, 11.64. Found: C, 45.01; H, 2.27; N, 12.17.

4-Amino-5-nitro-N-methylphthalimide (14).—4-Chloro-5-nitro-N-methylphthalimide (6.0 g, 25 mmoles) and 5.0 g of copper powder were suspended in 170 ml of diphenyl ether. This mixture was heated to 140–150° and ammonia gas was bubbled through with mechanical stirring for 24 hr. The copper powder was filtered off from the hot mixture, and the yellow precipitate which formed on cooling was recrystallized from methanol to give 1.5 g (6.8 mmoles, 27%) of the imide as yellow needles, mp 258° dec. An analytical sample was prepared by two more recrystallizations from ethanol: mp 255–262° dec; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 254 mμ (log ϵ 4.11), 283 (sh) (3.81), 330 (3.61), and 415 (3.45).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 19.00. Found: C, 49.02; H, 3.22; N, 19.43.

4,5-Diamino-N-methylphthalimide (15).—4-Amino-5-nitro-N-methylphthalimide (0.22 g, 1.0 mmole) in 50 ml of ethanol was catalytically reduced with hydrogen at atmospheric pressure in the presence of 50 mg of 10% Pd–C. In 70 min, 3 molar equiv

(13) E. H. White, "Light and Life," The Johns Hopkins Press, Baltimore, Md., 1961.

(14) J. Lee and H. H. Seliger, *Photochem. Photobiol.*, **4**, 1015 (1965).

(15) E. E. Ayling, *J. Chem. Soc.*, 253 (1929).

(16) W. A. Noyes and P. K. Porter "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1964, p 457.

(17) A. Ree, *Ann.*, **233**, 216 (1886).

(18) May & Baker Ltd., Belgian Patent 609,488 (April 21, 1961); *Chem. Abstr.*, **57**, 13695 (1962).

of hydrogen was absorbed and the reduction had stopped. Recrystallization of the product from methanol gave 0.169 g (0.88 mmole, 88%) of the diamino compound in the form of yellow needles, which showed only a single spot by tlc on silica gel. An analytical sample prepared by one more recrystallization from methanol decomposed at 258°: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 234 mμ (log ε 3.62), 278 (4.66), and 325 (3.40).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.56; H, 4.66; N, 22.23.

Quinoxaline-6,7-dicarbo-N-methylimide (16).—4,5-Diamino N-methylphthalimide (0.80 g, 4.1 mmoles) was dissolved in 150 ml of hot ethanol and a solution of 1.6 g of 30% glyoxal in 20 ml of ethanol was added. This mixture was heated on a water bath for 20 min under nitrogen, then kept in an ice box for 1 day to give the product in the form of pale brown needles. Repeated recrystallization from ethanol gave 0.66 g (3.1 mmoles, 74%) of quinoxaline **16** as pale brown needles, mp 210–211° dec. An analytical sample was prepared by further recrystallization from ethanol: mp 211–212° dec; ultraviolet $\lambda_{max}^{95\%EtOH}$ 259 mμ (log ε 4.17), 290 (sh) (3.69), 323 (3.04), and 338 (2.70); infrared (KBr) 1770, 1725 cm^{-1}.

Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.15; H, 3.55; N, 19.48.

1,2,3,4-Tetrahydroquinoxaline-6,7-dicarbo-N-methylimide (17).—Quinoxaline **16** (44 mg) was catalytically reduced with hydrogen in the presence of 0.2 g of PtO_2 in 15 ml of ethanol at atmospheric pressure. In 45 min, 2 molar equiv of hydrogen had been absorbed. The catalyst was filtered off and evaporation of the solvent gave 43 mg (0.19 mmole, 96%) of tetrahydroquinoxaline **17** in the form of orange needles, which gave a single spot by tlc on silica gel. An analytical sample was prepared by two recrystallizations from ethanol: mp 286° with sintering, 294–296° dec; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 248 mμ (log ε 3.46), 293 (4.29), and 343 (3.11).

Anal. Calcd for $C_{11}H_{11}N_2O_3$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.74; H, 5.24; N, 19.67.

1,4-Dimethyl-1,2,3,4-tetrahydroquinoxaline-6,7-dicarbo-N-methylimide (18).—A mixture of imide **17** (0.10 g, 0.5 mmole), 0.4 ml of methyl iodide, and 0.5 g of potassium carbonate in 20 ml of acetone was refluxed on a water bath for 24 hr. Additional methyl iodide (0.3 ml) and 0.4 g of potassium carbonate were added and the mixture was refluxed for an additional 30 min. The red reaction mixture was filtered while hot, and the filtrate was evaporated to dryness to give a red residue which was extracted with benzene. The benzene extract was evaporated to dryness to give red needles which were recrystallized from methanol to give 72 mg (0.29 mmole, 59%) of the product, mp 170–172°. An analytical sample was prepared by sublimation at 140° and 10^{-2} torr to give a product melting at 170–172°: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 260 mμ (log ε 4.11), 296 (4.58), and 340 (3.64).

Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.72; H, 5.85; N, 17.54.

1,2,3,4,7,8-Hexahydro-1,4-dimethylpyridazino[4,5-*g*]quinoxaline-6,9-dione (8).—A solution of imide **18** (31 mg, 0.126 mmole) in 0.5 ml of 95% hydrazine was heated on a water bath for 1 hr. The reaction mixture was allowed to stand at room temperature for 2 hr to give 9 mg of hydrazide **8**, which was paper chromatographically pure. The mother liquor was evaporated to dryness to give white needles which were purified by recrystallization from ethanol at Dry Ice temperatures. The precipitate was pure hydrazide **8**, as shown by paper chromatography. The total yield was 30 mg (0.12 mmole, 96%). Repeated purification by this method gave a sample that sintered at 298° and decomposed at 310°: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 276 mμ (log ε 4.68), 285 (sh) (4.64), and 354 (4.08).

Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.41; H, 6.11; N, 22.20.

1,2,3,4,7,8-Hexahydropyridazino[4,5-*g*]quinoxaline-6,9-dione (19).—Imide **17** (74 mg, 0.34 mmole) was treated with 0.3 ml of 95% hydrazine at 100° for 45 min. Hydrazine (2 ml) was added and the solution was heated on a water bath for an additional 75 min. The reaction mixture was allowed to stand at room temperature overnight to give colorless plates of the product (71 mg, 0.32 mmole, 95%). An analytical sample was prepared by three recrystallizations from acetic acid to give the solvate with 2 moles of acetic acid, which sintered at 280° but did not melt below 310°.

Anal. Calcd for $C_{10}H_{10}N_4O_5 \cdot 2CH_3COOH$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.62; H, 5.55; N, 16.86.

4-Amino-3,5-dinitro-N-methylphthalimide (20).—4-Amino-N-methylphthalimide (5.0 g, 29 mmoles) was dissolved in 37 ml of ice-cold concentrated sulfuric acid. To this solution was added dropwise in 1 hr an ice-cold mixture of 70% nitric acid (20 ml), water (0.5 ml), and concentrated sulfuric acid (10 ml). This reaction mixture was kept at 5° for 6 hr, then poured onto ice water to give a yellow precipitate. This material was treated with Norit and recrystallized from benzene. The product, 1.48 g (5.5 mmoles, 19%) was obtained as yellow needles, mp 225–228° dec. Repeated recrystallization from benzene gave a sample that had mp 228–228.5° dec; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 247 mμ (log ε 4.30), 270 (4.19), 318 (3.81), and 422 (3.72); nmr, singlets at τ 1.36 and 7.05 (weight ratio 1:3).

Anal. Calcd for $C_9H_6N_4O_6$: C, 40.61; H, 2.27; N, 21.05. Found: C, 40.78; H, 2.53; N, 20.67.

An attempted nitration of the imide with 70% nitric acid alone led to the recovery of 72% of the starting material. The use of 90% nitric acid led to an intractable product mixture.

3,4,5-Triamino-N-methylphthalimide (21).—4-Amino-3,5-dinitro-N-methylphthalimide (1.0 g, 4.28 mmoles) was suspended in 300 ml of methanol and catalytically hydrogenated in the presence of 0.1 g of 10% Pd–C. Within 6 hr, 6 molar equiv of hydrogen had been absorbed and the reaction was over. The reaction product was recrystallized from methanol to give 0.74 g (3.59 mmoles, 84%) of yellow needles, which gave a single spot by tlc on silica gel. An analytical sample was prepared by three recrystallizations from methanol to give a product sintering at 270° and decomposing at 280°: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 225 mμ (log ε 4.42), 285 (4.28), and 411 (3.80); nmr singlets at τ 3.28 and 7.01 (weight ratio 1:3), plus broad bands at τ 4.18 and 4.88 (weight = 6 (in CD_3SOCD_3)].

Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.31; H, 4.79; N, 27.09.

5-Aminoquinoxaline-6,7-dicarbo-N-methylimide (22).—To a hot solution of triamino compound **21** (0.22 g, 1.0 mmole) in 80 ml of water was added a hot aqueous solution of glyoxal–sodium bisulfite (0.3 g of the bisulfite adduct in 5 ml of water). This mixture was refluxed for 1 hr under a nitrogen atmosphere. The yellow precipitate was collected, and the red mother liquid was boiled again until more yellow material appeared. The combined yellow product was recrystallized from benzene to give 93 mg (0.4 mmole, 38%) of the product in the form of yellow needles which melted with decomposition at 272–275°. Three further recrystallizations from benzene gave a sample that had mp 272–275° dec; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 233 mμ (log ε 4.33), 292 (4.46), and 389 (3.83); infrared (KBr) 1750, 1700 cm^{-1}.

Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 58.12; H, 3.65; N, 23.47.

7,8-Dihydro-5-aminopyridazino[4,5-*g*]quinoxaline-6,9-dione (25).—Imide **22** (18 mg, 0.07 mmole) was suspended in 10 ml of 50% hydrazine and the mixture was heated on a water bath for 1 hr. The reaction mixture was evaporated to dryness to give a red powder which was then dissolved in 20 ml of ethanol. This ethanolic solution was condensed by half to give an orange precipitate (9 mg), which had a carbonyl peak at 1660 cm^{-1} in the infrared (typical for six-membered hydrazides). The compound was not obtained analytically pure.

1,2,3,4-Tetrahydro-5-aminoquinoxaline-6,7-dicarbo-N-methylimide (23).—Aminoquinoxaline **22** (69 mg, 0.3 mmole) in 20 ml of ethanol was catalytically reduced with H_2 in the presence of 50 mg of PtO_2. Two molar equivalents of hydrogen was absorbed in 10 min and the uptake then stopped. The catalyst was filtered off and the red filtrate was evaporated to dryness to give the product in the form of red needles, mp 255–260° dec. The yield was 52 mg (0.22 mmole, 74%). A sample, mp 255–260° dec, was prepared by sublimation at 210° and 10^{-2} torr: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 262 mμ (log ε 4.27), 298 (4.36), and 392 (3.80).

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 57.24; H, 5.00; N, 23.26.

1,2,3,4,7,8-Hexahydro-5-aminopyridazino[4,5-*g*]quinoxaline-6,9-dione (24).—Imide **23** (24 mg, 0.10 mmole) was treated with 0.3 ml of hydrazine on a boiling-water bath for 2 hr. To this pale brown mixture was added 1.5 ml of water and the mixture was heated on a water bath for 30 min. Evaporation of the reaction mixture gave the hydrazide as off-white needles (20 mg), which sintered at 265° and melted at 272° dec. We were unable to obtain an analytically pure sample.

The Benzimidazole Approach. A. 5,6-Dimethylbenzimidazole (27).—2-Amino-4,5-dimethylaniline (**26**) (1.36 g, 10 mmoles) in 0.87 g of 80% formic acid was heated on a boiling-water bath

for 2 hr, then cooled. Aqueous KOH (0.25 *N*) was added until the reaction mixture was turbid, the flask was cooled to 0°, and the colorless product was collected. Recrystallization from boiling water gave 1.01 g (7.4 mmoles, 74%) of **27** as colorless needles: mp 202–204° (lit.[19] 205–205°); nmr, singlets at τ 2.00, 2.55, and 7.62 in the ratio 1:2:6.

B. Oxidation of 5,6-Dimethylbenzimidazole (27).—Following the directions of Morgan,[20] 10.0 g (0.0685 mole) of 5,6-dimethylbenzimidazole was suspended in 2 l. of boiling water, and a solution of 43 g (0.272 mole) of potassium permanganate dissolved in 1 l. of water was added dropwise with constant stirring and heating (95°) over a period of 1 hr. The mixture was then boiled for 15 min, acidified with 100 ml of concentrated HCl, and then decolorized with sodium bisulfite. On cooling the solution for a few days at 4°, 6.61 g of the product separated as a white, crystalline mass. On concentration to half-volume, an additional 1.1 g was obtained. The product was dried at 100° and 0.05 torr: mp 320° (introduced in bath at 300°) (lit.[20] 322–324°); neut equiv 113; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 219 mμ (log ϵ 4.70), 265 (3.85). A sample was recrystallized from 80% aqueous ethanol (68% recovery), and the product was dried at 100° and 0.05 torr: nmr (in D_2O) τ 1.70 (singlet, 1 H), 2.26 (singlet, 1 H), 2.61 (singlet, 1 H), and 7.40 (singlet, 3 H). See nmr below for more accurate chemical shifts.

Anal. Calcd for $C_9H_6N_2O_4 \cdot H_2O$: C, 48.22; H, 3.60; N, 12.50. Calcd for $C_9H_8N_2O_2 \cdot 2H_2O$: C, 50.94; H, 5.70. Found: C, 47.30; H, 4.42.

This sample was recrystallized twice from an acetic acid–water mixture (9:1) and dried at 100° and 0.05 torr.

Anal. Found: C, 48.12; H, 4.09; N, 13.00.

A similar oxidation was carried out, but the basic mixture was filtered hot and evaporated to one-half volume. Extraction with ethyl acetate led to the recovery of 7% of the starting material.

Acidification with hydrochloric acid gave 4.11 g of a colorless powder, mp 275–288° dec, which on recrystallization from hot water gave 3.43 g of fine needles, mp >315° (sinters at 305°); this material was recrystallized from 90% aqueous acetic acid and then from water. Further concentration of the mother liquid yielded an additional 3.7 g of the acid [paper chromatography of both fractions with alcohol–ammonia–water (8:1:1) showed that both gave a single spot (dark by ultraviolet light, and acidic to indicators) at R_f 0.65]: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 220 mμ (log ϵ 4.63) and 265 (3.83); nmr (in D_2O), τ 2.00 (singlet, 1 H), 2.30 (singlet, 1 H), 2.54 (broadened singlet, 1 H), and 7.49 (singlet, 3 H).

Anal. Found: C, 47.96; H, 4.07; N, 12.02. Found: C, 47.57; H, 4.24; N, 11.83; Cl, 4.79 ($=C_{9.3}H_{10.0}N_{2.0}O_{4.7}Cl_{0.3}$).

This material, which gave a negative Beilstein test, was then recrystallized from 50% hydrochloric acid to yield small needles that did give a positive Beilstein test; mp 305–308° dec; infrared (KBr) 1720 cm^{-1}; ultraviolet $\lambda_{max}^{H_2O}$ 260 mμ (log ϵ 3.49), 277 (3.74), and 285 sh (3.73).

Anal. Calcd for $C_9H_8N_2O_2 \cdot HCl$: C, 50.83; H, 4.26; N, 13.17; Cl, 16.67. Found: C, 50.54; H, 4.37; N, 13.28; Cl, 16.50.

C. 4,5-Diacetylamino-2-methylbenzoic Acid (30).—The oxidation product (1.0 g, 6.1 mmoles) in 20 ml of acetic anhydride was boiled with 0.5 g of fused sodium acetate for 3.5 hr. The dark reaction mixture was poured into ice water and extracted three times with ethyl acetate. The aqueous part was allowed to stand at room temperature for 2 days to give 0.18 g of colorless needles A. The ethyl acetate extract was evaporated to dryness to give a dark oily residue. Ethanol was added to this oil to give a precipitate which was recrystallized from water to give colorless needles B. A was identical with B (as shown by paper chromatography using EtOH–NH_4OH–H_2O) and combined products A and B were recrystallized from water to give 0.58 g (2.3 mmoles, 38%) of **30** as colorless needles which melted at 258–259°. An analytical sample, mp 258–259°, was prepared by three recrystallizations from water.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.82; H, 5.72; N, 11.13.

D. 3,5-Dimethyl-6-carbomethoxybenzimidazol (32).—The oxidation product (0.30 g, 1.8 mmoles) was suspended in 30 ml of acetone and excess diazomethane in ether was added. The yellow solution was kept at room temperature for 0.5 hr; then acetic acid was added to give a colorless solution. The solution was washed with sodium bicarbonate and water and then dried. The ether was removed to give 0.14 g of a colorless, crystalline residue which was chromatographed on 4.5 g of silica gel using chloroform as the eluent. The first fraction was pure as shown by tlc; the product was recrystallized from carbon tetrachloride to give 62 mg (0.33 mmoles, 18%) of colorless needles, mp 86–87°. An analytical sample, mp 86.5–87°, was obtained by one more recrystallization from carbon tetrachloride: ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 215 mμ (log ϵ 4.35) and 261 (3.87).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.72; H, 6.10; N, 14.14.

E. 5-Methyl-6-carbomethoxybenzimidazole (31).—The oxidation product was refluxed in methanol containing sulfuric acid for 1 day to yield 67% of the ester, which was recrystallized from water: mp 144–145°; λ_{max} 220 mμ (log ϵ 4.78) and 265 (3.99); the neutralization equivalent by titration with perchloric acid in acetic acid was 192 (calcd 190); nmr singlets at τ −1.01 (broad), 1.57, 1.70, 2.43, 6.06, and 7.28 (weight ratio 1:1:1:1:3:3).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.59; H, 5.64; N, 14.24.

The Quinoxaline Approach. A. 6,7-Dimethylquinoxaline (33).—2-Amino-4,5-dimethylaniline (0.68 g, 5 mmoles) was suspended in a mixture of 2.5 ml of 2 *N* acetic acid and 4 *N* sodium acetate (1.25 ml). To this suspension, glyoxal bisulfite (1.4 g, 5 mmoles in 7.5 ml of H_2O) was added and the mixture was heated at 60° for 20 min. Ethanol was added to dissolve the floating material. The resulting solution was heated at 60° for 14 hr and the solvent was then removed under reduced pressure. Aqueous sodium bicarbonate was added to the residue and the mixture was extracted with ethyl acetate. After washing the solution with water and drying it, the solvent was removed to give pale yellow plates of the product (0.73 g, 4.6 mmoles, 92%), mp 95–98° (lit.[21] 100–101°). Sublimation yielded a colorless sample.

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.58; H, 5.89; N, 18.09.

B. Oxidation of 6,7-Dimethylquinoxaline.—Potassium permanganate (2.6 g, 16 mmoles in 70 ml of water) was added to a suspension of 6,7-dimethylquinoxaline (0.65 g, 4.0 mmoles) in 10 ml of water, and the mixture was boiled for 2.5 hr. The reaction mixture was filtered while hot and the dark cake on the filter was washed with dilute alkali. The combined filtrates were evaporated to a volume of about 30 ml under reduced pressure, then extracted twice with ethyl acetate. The ethyl acetate extract contained 65 mg (0.4 mmole, 10%) of the starting material. The aqueous part was acidified with dilute hydrochloric acid and the gray powder which precipitated was filtered, washed with water, and dried. The nmr spectrum of this product (40 mg) in D_2O–NaOD (external TMS) showed a singlet at τ 7.40 (3 H), an AB quartet at 1.60 (2 H, J = 2 cps),[22] a singlet at 2.28 (1 H), and a broadened singlet at 2.65 (1 H). A sample was prepared by three recrystallizations from methanol: mp 238–244° dec; ultraviolet $\lambda_{max}^{95\%\ EtOH}$ 244 mμ (log ϵ 4.26) and 327 (3.75).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.72; H, 4.44; N, 15.38.

The remaining acidic solution was then evaporated to dryness and the dark powder formed was extracted with hot acetone. Evaporation of the acetone and recrystallization of the solid from water (after a treatment with Norit) yielded large prismatic crystals, mp 160–164°, and smaller crystals, mp 120–122° (the structures of these compounds is unknown).

Dimethyl 4-Dodecanethiophthalate (37).—A solution of potassium *t*-butoxide in *t*-butyl alcohol (4.2 ml of 1.2 *N*, 5.04 mmoles) was placed in a Pyrex tube and 1.01 g (5.0 mmoles) of dodecanethiol was added; a colorless precipitate formed. The alcohol was distilled *in vacuo*; then 1.1 g (5.0 mmoles) of dimethyl 4-chlorophthalate (**36**) and dry dimethylformamide (4.5 ml) were added. The tube was sealed off and then heated on a steam bath for 48 hr. The reaction mixture was dissolved in ethyl acetate and washed with water and diluted sodium hydroxide solution. The ethyl acetate was distilled to give 1.5 g of a yellow oil, which was chromatographed on silica gel.

(19) N. G. Brink and K. Folkers, *J. Am. Chem. Soc.*, **71**, 2951 (1949).

(20) Private communication from Dr. K. J. Morgan.

(21) J. K. Landquist, *J. Chem. Soc.*, 2816 (1953).

(22) A coupling constant of 1.7 cps has been reported for similar protons in pteridines [S. Matsuura and T. Goto, *J. Chem. Soc.*, 1773 (1963)].

The second fraction of the chloroform eluate contained the desired product, which was recrystallized from ligroin to give (1.0 g, 2.5 mmoles, 50%) of **37** as colorless crystals, mp 35–36°. An analytical sample was prepared by further recrystallization from ligroin: mp 35–36°; ultraviolet $\lambda_{max}^{95\% EtOH}$ 237 mμ (log ε 4.07) and 287 (4.09); nmr singlet τ 6.12, OCH_3) and complex multiplet centered at τ 8.7.

Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.98; H, 8.69. Found: C, 67.16; H, 8.63.

4-Dodecanethiophthalic acid was prepared by the hydrolysis of dimethyl ester **37** with hot aqueous alkali followed by acidification. Recrystallization from benzene yielded crystals melting at 110–110.5°.

Anal. Calcd for $C_{20}H_{30}O_4S$: C, 65.55; H, 8.25. Found: C, 65.54; H, 8.19.

6-Dodecanethio-2,3-dihydro-1,4-phthalazinedione (38).—A mixture of dimethyl 4-dodecanethiophthalate (0.84 g, 2.1 mmoles) in 0.3 g of 95% hydrazine was heated on a boiling-water bath for 24 hr. The reaction product was washed with water, then recrystallized from acetic acid to give the hydrazide as colorless needles (0.66 g, 1.8 mmoles, 85%), mp 185°. An analytical sample was prepared by two recrystallizations from acetic acid: mp 186–188.5° (sinters at 180°); ultraviolet $\lambda_{max}^{95\% EtOH}$ 230 mμ (sh) (log ε 4.08), 240 (sh) (4.00), and 282 (4.31).

Anal. Calcd for $C_{20}H_{30}N_2O_2S$: C, 66.27; H, 8.37; N, 7.73. Found: C, 66.59; H, 8.47; N, 7.84.

Registry No.—**8**, 10351-64-1; **13**, 5566-47-2; **14**, 10351-66-3; **15**, 10351-67-4; **16**, 10351-68-5; **17**, 10378-07-1; **18**, 10351-69-6; **19**, 10351-70-9; **20**, 10351-71-0; **21**, 10351-72-1; **22**, 10351-73-2; **23**, 10351-74-3; **27**, 582-60-5; **28**, 10351-75-4; **29**, 10351-76-5; hydrochloride of **29**, 10351-77-6; **30**, 10351-78-7; **31**, 10351-79-8; **32**, 10351-80-1; **33**, 7153-23-3; **34**, 10351-82-3; **37**, 10351-83-4; **38**, 10351-84-5; 4-dodecanethiophthalic acid, 10351-85-6.

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Reactions of Alkoxysulfonium Salts with Alkoxides[1,2a]

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The reaction of representative alkoxysulfonium salts with a variety of alkoxides has been examined. The salts were found to undergo rapid alkoxy exchange followed by (a) base-catalyzed collapse to carbonyl compounds and sulfides or (b) α rearrangements (analogous to the Pummerer reaction) to produce monothioacetals. An ylide appears to be a common intermediate in these reactions. Appropriate deuterium-labeling experiments reveal that the elimination to carbonyl compounds proceeds *via* a cyclic transition state involving the sulfur ylide. The preponderance of the α-rearrangement reaction appears to be a function of the stability of the carbonium ion formed *via* elimination of alkoxide from the ylide intermediate. In all cases the ylide reacts rapidly in the manners stated and is not reprotonated to any significant extent.

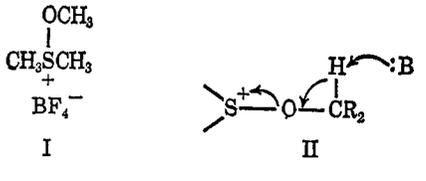
A number of synthetically intriguing oxidation reactions that depend on the intervention of alkoxysulfonium salts have now been developed. Halides and tosylates are oxidized by dimethyl sulfoxide (DMSO) at elevated temperatures to the corresponding carbonyl compounds;[3] alcohols are converted to aldehydes or ketones by DMSO and dicyclohexylcarbodiimide under acid–base catalysis;[4] similar reactions can be initiated between alcohols and dimethyl sulfoxide in the presence of acetic anhydride[5] or phosphorus pentoxide[6] or by prior conversion of the alcohol to a chloroformate.[7] These reactions are schematically summarized by eq 1.

$$R_2CHX + CH_3\overset{\overset{O}{\|}}{S}CH_3 \longrightarrow CH_3\overset{\overset{OCHR_2}{|}}{\overset{+}{S}}CH_3\ X^- \longrightarrow R_2C{=}O + CH_3SCH_3 + HX \quad (1)$$

The collapse of the intermediate alkoxysulfonium salts to carbonyl compounds and sulfide is promoted by base. The present paper is concerned with the reactions of isolated and characterized alkoxysulfonium salts with alkoxides.[8] The results have a mechanistic bearing on the above-described reactions and are of preparative and interpretive significance.

Results and Discussion

Exchange Reactions.—The reaction of simple alkoxysulfonium salts with alkoxides proceeds with rapid exchange of the alkoxy group followed by base-catalyzed elimination to provide carbonyl compounds. When dimethylmethoxysulfonium fluoroborate (I) labeled with carbon-14 in the O-methyl group was treated with sodium hydride in dimethyl sulfoxide, correspondingly labeled formaldehyde was obtained; however, when sodium methoxide in methanol was employed as the base the formaldehyde exhibited less than 1% of the radioactivity of the starting salt. The formaldehyde was characterized and its radioactivity determined as the methone. Exchange was also dictated by the observation that when the reaction was run part-



I

II

(1) (a) Part VII in the series Chemistry of Sulfoxides; (b) part VI, C. R. Johnson and M. P. Jones, *J. Org. Chem.*, **32**, 2014 (1967).

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